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Effect of traumatic imagery on cerebrospinal fluid dopamine and serotonin metabolites in posttraumatic stress disorder

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ABSTRACT

Dopaminergic mechanisms may be involved in the pathophysiology of posttraumatic stress disorder (PTSD), although the evidence for this is limited; serotonergic mechanisms are implicated largely by virtue of the modest efficacy of serotonergic drugs in the treatment of the disorder. Basal cerebrospinal fluid (CSF) dopamine and serotonin metabolite concentrations are normal in PTSD patients. However, in the present experiment, we postulated that perturbations in CSF dopamine and serotonin metabolites could be induced by acute psychological stress. Ten volunteers with war-related chronic PTSD underwent 6-h continuous lumbar CSF withdrawal on two occasions per patient (6–9 weeks apart), using a randomized, within subject-controlled, crossover design. During one session a 1-h video with trauma-related footage (traumatic video) was shown and in the other session subjects viewed a 1-h neutral video. We quantified the dopamine metabolite homovanillic acid (HVA) and the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in CSF at 10-min intervals, before, during, and after video provocation. Blood pressure, heart rate, and subjective anxiety and mood were monitored. Significant drop in mood and increases in anxiety and blood pressure occurred during the traumatic relative to the neutral movie. CSF HVA concentrations diminished significantly after the traumatic video ($p < 0.05$), in comparison with the neutral, while 5-HIAA tended to diminish ($p < 0.10$). We conclude that an acute decline in CNS HVA concentrations is associated with laboratory-induced symptoms in chronic PTSD patients. While further research is required to determine if the stress-induced dopaminergic changes are normative or pathological, the present data suggest that increasing dopaminergic neurotransmission be explored as a potential therapy, or adjunctive therapy, for PTSD.

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1. Introduction

Dopaminergic mechanisms may be involved in the pathophysiology of posttraumatic stress disorder (PTSD), but the evidence for this is limited. Investigations of dopaminergic candidate genes have yielded inconsistent, inadequately replicated, negative, or contradictory, results (for example, see Broekman et al., 2007 for a review and, more recently, Bailey et al., 2010; Valente et al., 2011). Clinically, dopamine D_2 receptor antagonists may reduce certain symptoms in PTSD patients who manifest them, such as insomnia/hyperarousal (Stein et al., 2002; Rothbaum et al., 2008; Krystal et al., 2011) and/or psychotic symptoms (Hamner et al., 2003), but data on their general efficacy in PTSD are, to date, negative (Krystal et al., 2011). Conversely, although dopamine signal-promoting drugs have not been rigorously tested in PTSD, a few clinical cases of psychostimulant-induced improvements have been reported, one in a woman with car accident-related PTSD after phenethylamine diethylpropion for weight loss was added to a standing dose of fluoxetine (Daly, 2000) and three in combat veterans who were prescribed methylphenidate (in one case supplemented with dextroamphetamine) (Houlihan, 2011). However, it should be noted that diethylpropion, methylphenidate, and amphetamine all increase noradrenergic as well as dopaminergic signaling (Raiteri et al., 1975; Geranton et al., 2003; Kuczenski and Segal, 2005; Arnsten, 2006; Han and Gu, 2006; Santamaria and Arias, 2010).

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A role for serotonin in the pathophysiology of PTSD is most strongly supported by the palliative effects of serotonergic drugs in the disorder. Serotonin-reuptake inhibitors, such as fluoxetine, sertraline, and paroxetine, ameliorate symptoms in many civilian patients with PTSD (van der Kolk et al., 1994; Brady et al., 2000; Davidson et al., 2001; Marshall et al., 2001) – although marginal benefit of serotonin-reuptake inhibitors in military combat-related PTSD is typically seen (van der Kolk et al., 1994; Hertzberg et al., 2000; Zohar et al., 2002).

In prior work we observed no differences in basal cerebrospinal fluid (CSF) and plasma concentrations of the major dopamine and serotonin metabolites, homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA), respectively, between combat veterans with PTSD and healthy comparison subjects (Geracioti et al., 1999; Strawn et al., 2002). However, examination of stress-induced effects on CSF 5-HIAA and HVA in PTSD (and in humans in general) has heretofore been lacking. This has been an important limitation. In the same way that suspected abnormalities in coronary artery blood flow or in glucose tolerance often require, respectively, a cardiac stress test or glucose tolerance test to elicit, CNS monoaminergic abnormalities in PTSD might be occult, manifesting only during stress.

To examine the effects of acute psychological stress on CNS dopamine and serotonin systems in patients with chronic combat-related PTSD, we combined continuous cerebrospinal fluid sampling, via an indwelling subarachnoid catheter, with exposure – in random order on two separate testing days – to either a 60-min stress-inducing video containing traumatic imagery or to a neutral videotape. By waiting for 2.5–3 h after placement of the thin, flexible subarachnoid catheter, and after removal of the needle used to place it, the neurohormonal response to the stress of the procedure resolves before CSF sampling starts (Hill et al., 1999).

2. Patients and methods

2.1. Patients

This study was approved by the Institutional Review Board of the University of Cincinnati Medical Center and by the Research and Development Committee of the Cincinnati Veterans Affairs Medical Center (VAMC). Written, informed consent was given by each patient prior to his participation in the study.

Ten male volunteers with combat-related, chronic post-traumatic stress disorder were enrolled in the study. Eight of these volunteers each completed two 6-h continuous CSF sampling procedures on separate days 6–9 weeks apart (except for one of the patients, who went five months between procedures) and data analysis was restricted to the results from these eight individuals (4 Army, 4 Marines). Mean Clinician-Administered PTSD Scale (CAPS) scores (Blake et al., 1995) were 79 ± 22 and 86 ± 19 the day before the traumatic and neutral videos, respectively. Two patients had comorbid clinical diagnoses of major depression, while all others had mild to moderate depressive symptoms. The Hamilton Depression Scale (Hamilton, 1960) was 12 ± 8 and 14 ± 11 the day before the traumatic and neutral videotape sessions, respectively.

Nicotine aside, seven of the eight evaluable subjects had a history of substance dependence or abuse, but all seven of these had been abstinent from alcohol or drugs of abuse, by history, for an average of 40 months (range 3–216 months). Urine drugs screens were negative in the enrolled patients. However, three of the patients smoked tobacco and were nicotine dependent at the time of study; two others were former smokers.

All subjects were medication free, for a minimum of more than five medication disappearance half-lives, prior to undergoing the CSF sampling procedure.

2.2. Procedures

Subjects were admitted to the Psychoneuroendocrinology Unit of the Cincinnati VA Medical Center the day before each videotape exposure. Psychological ratings, diet, fluids, smoking, intravenous catheter placement, and activity were strictly controlled, as previously described (Geracioti et al., 2008). The next morning, a 20-gauge polyamide catheter was placed in the subarachnoid space (spinal canal) between 0800 and 0830 h, also as described previously (Geracioti et al., 2008). Continuous CSF collection began at 11:00 h at a rate of 0.1 mL per minute using a peristaltic pump. CSF was collected for 6 h (until 1700 h) into a series 36 iced test tubes that were flash-frozen on dry ice at bedside at 10-min intervals. Saline solution was infused at 100 mL/h throughout the procedure.

2.3. Videos

To evoke traumatic reminiscence during one of these procedures a 60-min stress videotape with combat and war injuries (traumatic video) was shown whereas during the other CSF sampling procedure subjects viewed a 60-min neutral videotape (oil painting instructional), according to a randomization schedule (see Geracioti et al., 2008). Videos commenced at 1200 h, 1 h after the start of continuous CSF and serial blood withdrawal.

2.4. Subjective anxiety, mood, and hunger ratings

Anxiety ("nervousness") and mood were self-rated at 10-min intervals throughout each procedure, using 100-mm visual analog scales (Aitken and Zeally, 1970). The analog scale anchors were "high" and "low" for both scales.

2.5. Hormonal and neurochemical analyses

Samples from a given subject obtained during both the neutral and traumatic sessions were paired and run in a single assay for each neurochemical. Each neurochemical was assayed in duplicate. CSF HVA and 5-HIAA concentrations were quantified by HPLC with electrochemical detection using previously reported methods (Geracioti et al., 1999; Strawn et al., 2001). The intra-assay coefficient of variation was 4.0% for HVA and 2.9% for 5-HIAA. Respective inter-assay coefficients of variation (*cv*) were 5.1%, and 3.7%.

2.6. Statistical analysis

For both the neutral and traumatic video sessions, the difference between measures of subjective anxiety, subjective mood, and CSF monoamine metabolites from their mean baseline values (1100–1200 h) were calculated and compared using repeated-measure analyses of variance. That is, using paired comparisons (traumatic vs. neutral), data were examined for relative changes from the mean baseline values; baseline means were therefore equal to 1.0 and subsequent relative change values were calculated by dividing by the corresponding baseline value. Relative changes that were not normally distributed were log transformed prior to using multivariate, repeated measures analysis of variance (ANOVA). For each subject during each movie the difference in the anxiety rating was taken between successive 10-min intervals. These differences approximated instantaneous changes, or slope, in anxiety during the movie. In each case the maximum of these differences was computed, and for each subject the difference between these maximum slopes for the two films, Vietnam minus Neutral, was computed. These differences were compared using Wilcoxon Signed-Rank test. Pearson coefficients were used in all correlation analyses. p values <0.05 were considered significant.